REMARKS

Pending Claims

Claims 1-17 are pending, and claims 19-51 are withdrawn as directed to the nonelected invention. Claim 18 was formerly canceled. Claim 1 has been amended to incorporate the limitation of claim 3, canceled herein. Claim 4 has been amended to correct dependency in view of the cancellation of claim 3. Claims 1 and 20 are amended to delete "or more" and to recite "a" level of natriuretic peptide. Newly added claim 52 is supported by the disclosure on specification page 11, line 27, though page 12, line 2. Newly added claim 53 is supported by the disclosure on specification page 19, lines 11-18. The amendments are fully supported by the specification as originally filed.

The Office Action

The Office Action sets forth four grounds for rejection of the subject application:

(1) claims 1-17 and 19-36 are provisionally rejected over claims 1-36 of copending application 11/248,650 on the basis of purported obviousness-type double patenting;

(2) claims 1-17 and 19-36 are rejected under 35 U.S.C. § 103 over Bergmann et al. (U.S. Patent 5,541,116) in view of each of Chen (U.S. Patent 6,525,102) and Flaa (PCT International Application WO 96/27661);

(3) claims 10, 11, 27 and 28 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide enablement for "a stabilizing compound", a "biocide", a "protein", and "a polymer"; and

(4) claims 1-17 and 19-36 are rejected under 35 U.S.C. § 112, second paragraph, as purportedly being indefinite.

Applicants request that the Examiner reconsider the grounds for rejection as discussed in the following paragraphs.

Patentable Distinctness of the Application Claims

Claims 1-17 and 19-36 are provisionally rejected over claims 1-36 of copending application 11/248,650. Applicants will file a terminal disclaimer in the second allowed case if the allowed claims of the second application are not patentably distinct from the allowed claims of the first granted application.

Nonobviousness of the Application Claims

The Office Action alleges that claims 1-17 and 19-36 are obvious over Bergmann et al. in view of each of Chen and Flaa. The Office Action acknowledges that Bergmann et al. fails to teach the pH limitations of the independent claims of the subject application, as well as the additional stabilizing substances set forth in some of the dependent claims. The Office Action argues, however, that it would have been obvious to stabilize peptides as taught by Bergmann et al. at the pH ranges and with the additional substances taught by each of Chen and Flaa because both Chen and Flaa teach stabilizing various polypeptides for the same function as claimed at the pH range and with the substances as presently claimed. This rejection is respectfully traversed.

Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, both a suggestion to make the composition or carry out the claimed process, and a reasonable expectation of success must be found in the prior art to support a conclusion that a patent application claim is obvious. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). An invention is not obvious over the prior if the prior art does not suggest each and every limitation of the claim. Under § 103, a prior art reference that fails to teach toward the claimed invention, or teaches away from the claimed invention, will not render the invention as claimed obvious. The application of the law to the facts of this case are discussed below.

a. Failure of the references to suggest all the claim limitations

There is nothing in the disclosure of Bergmann et al. alone or in combination with that of Chen and Flaa to teach or suggest (a) a "stable liquid calibrator or control", (b) having a pH "of from about 4.0 to about 6.5", and/or (c) "wherein the calibrator or control remains stable when stored at temperatures of from about 2 to about 8°C for a period of about twelve (12) months", and the Office Action does not provide any evidence to the contrary.

Bergmann et al. relies for stabilization of blood peptides in patient samples on the addition of a combination of the proteolysis inhibitors amastin and leupeptin and ethylenediaminetetraacetic acid (EDTA). By contrast, the calibrators or controls of the invention are not patient samples, but comprise an artificial matrix. The use of proteolysis inhibitors in the calibrators and controls of the invention is optional (e.g., discussed at page 8, line 29, through page 9, line 19). As discussed in the subject application, "the key to the stability of the calibrators and controls of the present invention is pH" (page 11, lines 17-18). Bergmann et al. thus in no way teaches or suggests the criticality in calibrators or controls of

having a pH "of from about 4.0 to about 6.5" for stabilization of the natriuretic peptide, much less teach or suggest a calibrator or control that is stable "for a period of about twelve (12) months."

The secondary references Chen and Flaa provide no teachings which cure the deficit of Bergmann et al. Chen discloses stabilization of aqueous pharmaceutical compositions of polypeptides by avoiding the problem of polypeptide aggregation and/or deamidation (glutamine or asparagine) by inclusion in the pharmaceutical composition of the combination of an amino acid base buffered by an acid substantially free of its salt form. Chen clearly recognizes that the optimum pH for stability of a particular polypeptide of interest needs to be determined empirically (e.g., column 10, lines 1-7). Chen provides no information, however, regarding the optimum pH for stability of natriuretic peptides in an artificial matrix.

Likewise, Flaa provides no more than a broad brush teaching that an artificial matrix can be derived for troponin, myoglobin, CK, CK isoenzymes, LD, LD isoenzymes, myosin, and fragments thereof, and speculates that such a matrix can be derived for other cardiac markers. A chelating agent in the matrix is required by Flaa (e.g., page 7 lines 18-24, and page 10, lines 23-29), and includes EDTA. Such chelating agents of Flaa thus appear to correspond to the proteolysis inhibitors of Bergmann et al., which means Flaa adds little, if anything, over the teachings of Bergmann et al. Flaa, like Chen, fails to provide information regarding the optimum pH for stability of natriuretic peptides in an artificial matrix.

In sum, the teachings of Bergmann et al., Chen, and Flaa considered in combination would do no more than, at best, inviting one to further experimentation on an artificial matrix for natriuretic peptides. Such obviousness to ***try*** to obtain the subject invention is not obviousness under 35 U.S.C. § 103. The references alone or in combination fail to teach or suggest (a) a "stable liquid calibrator or control", (b) having a pH "of from about 4.0 to about 6.5", and/or (c) "wherein the calibrator or control remains stable when stored at temperatures of from about 2 to about 8°C for a period of about twelve (12) months" as is required for a finding of obviousness.

b. Lack of motivation to combine the prior art's teachings

Bergmann et al. provides a means for stabilization in ***blood samples***, Chen discloses stabilization of ***aqueous pharmaceutical compositions***, and Flaa provides at best stabilization in an ***artificial matrix***. Bergmann et al. provides for stabilization by inclusion of proteolysis inhibitors, Flaa by inclusion of a specific type of proteolysis inhibitor (chelating agents such as EDTA), and Chen by the combination of an amino acid base buffered by an acid

substantially free of its salt form. The three references thus use distinctly different liquid compositions along with different methods of addressing the issue of stabilization. Based on this, one of ordinary skill clearly would lack motivation to combine the disclosure of Bergmann et al. with the teachings of Chen and Flaa. Of course, absent such motivation to combine, the obviousness rejection is not supported.

c. The prior art's teaching away from the subject invention

Moreover, the prior art disclosures in fact defy combination such that the subject invention can be obtained. This is because Bergmann et al. in its reliance for stabilization on proteolysis inhibitors, Flaa in its reliance of chelating agents, and Chen in its reliance on the combination of an amino acid base buffered by an acid substantially free of its salt form, ***teach away*** from the subject invention. Even if the teachings are combined, the closest to the invention that is obtained are calibrators and controls in which the natriuretic peptide is stabilized by proteolysis inhibitors and which arguably fall within the pH range recited in the claims and may include additional stabilizing substances set forth in some of the dependent claims. This is <u>not</u> the subject invention.

For at least the reasons given above, applicants respectfully submit that the obviousness rejection is unwarranted and request that it be withdrawn. The applicants submit that the obviousness rejection also is not applicable to newly added claims 52 and 53, and request that it not be so applied.

<u>Enablement of the Application Claims</u>

Claims 10, 11, 27 and 28 are rejected because while the specification is enabling for certain specific reagents, the specification allegedly does not provide enablement for "a stabilizing compound", a "biocide", a "protein", and "a polymer", and it would purportedly require undue experimentation to determine which such substance would work in the invention. Applicants respectfully traverse the rejection.

Applicants disclose how to make and use the calibrators and controls of the invention where the stabilizing compound is a protein or a polymer (claims 11 and 28), and where the diluent comprises a biocide in addition to a stabilizing compound (claims 10 and 27). In particular, the specification discloses stabilizing proteins and polymers that include but are not limited to bovine serum albumin, bovine gamma globulin, non-fat dry milk, polyethylene glycol, dextran, dextran sulfate, and polyvinyl pyrrolidone (e.g., page 5, lines 11-14).

Additional examples of stabilizing proteins/polymers and defining features of such proteins/polymers are described at page 8, line 29 through page 9, line 19. Examples of biocides and defining features of such biocides are described at page 9, lines 21 through 31. The application further advises that in addition to custom made diluents in which stabilizing proteins/polymers and biocides optionally are employed, at the discretion of the practitioner, a commercially-available diluent comprising stabilizing proteins/polymers and biocides can be used instead of or in combination with custom made diluents (e.g., page 8, lines 18-24, page 10, 25-29). The application provides examples including use of stabilizing proteins/polymers and biocides (e.g., Examples 1-3). Moreover, stabilizers (proteins/polymers) and biocides are in widespread use in calibrators and controls such that further information is available to the skilled artisan in employing these substances in the calibrators and controls of the invention.

In *In re Wands*, the Federal Circuit held that undue experimentation is determined by a standard of reasonableness which can be assessed by examining eight factors: (1) quantity of experimentation necessary (both in terms of time and expense); (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

With respect to *Wands* factors (2) and (3), the specification provides direction and guidance for stabilizers (proteins/polymers) and biocides as discussed previously, as well as working examples. The time and expense necessary to use other stabilizers (proteins/polymers) and biocides in the calibrators and controls of the invention, as addressed by factor (1), is minimized in view of the specification disclosure and information available in the art. Adaptation for other stabilizers (proteins/polymers) and biocides is routine. In accordance with *Wands* factor (7), and as discussed in the specification (e.g., at page 11, lines 16-21), the ordinary skilled artisan would predict the effectiveness of a wide variety of other stabilizers (proteins/polymers) and biocides in the calibrators and controls of the invention provided pH is appropriately controlled. The breadth of the present claims is appropriate, as addressed by *Wands* factor (8), since the claims encompass results which clearly have been demonstrated (i.e., stable calibrators and controls, optionally using stabilizing proteins/polymers and biocides) and which are not expected to vary with use of other appropriate stabilizing proteins/polymers and biocides. As regarding *Wands* factors (4)-(6),

the ordinary skilled artisan is well versed in the use of stabilizers (proteins/polymers) and biocides.

For at least the foregoing reasons, the skilled artisan clearly could make and use the invention as presently claimed, and further, could do so without undue experimentation. Therefore the applicants respectfully assert that the enablement rejection is unwarranted and request that it be withdrawn.

Definiteness of the Application Claims

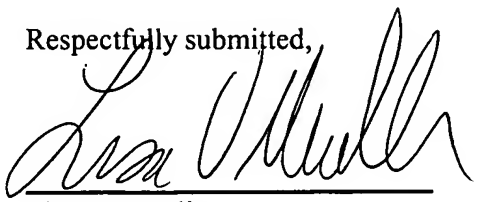
Claims 1-17 and 19-36 are rejected under 35 U.S.C. § 112, second paragraph, as purportedly being indefinite because in claim 1, line 2, "the level" lacks antecedent basis, and because in claim 1, last line, "12 months or more" allegedly reads on infinity.

Claims 1 and 20 are amended herein to delete "or more". The amendment is made not in acquiescence to any pending rejection, but merely, at the discretion of applicants, to delete a less preferred embodiment of the invention. Furthermore, claims 1 and 20 are amended herein to recite "a" level of natriuretic peptide. Again, the amendment is made not in acquiescence to any pending rejection, but merely to correct an inadvertent typographical and grammatical error (which applicants thank the Examiner for noting).

CONCLUSION

For at least the foregoing reasons discussed above, the subject application is believed to be in good and proper form for allowance. The Examiner is therefore requested to pass this application to issue. If, in the opinion of the Examiner, a telephonic interview would expedite the prosecution of the present application, the Examiner is invited to contact applicants' undersigned attorney.

Respectfully submitted,



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